DM

Disease-a-Month Series

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Max Miller—DIABETES MELLITUS
William J. Harrington—THE PURPURAS
Donald W. Seldin—ELECTROLYTE DISTURBANCES IN CONGESTIVE HEART FAILURE
Michael E. DeBakey—PERIPHERAL ARTERIAL INSUFFICIENCY
Harley C. Shands—ANXIETY STATES
John R. Graham—HEADACHE
J. Walter Wilson—SYSTEMIC FUNGUS INFECTIONS
Philip K. Bondy—NON-TOXIC GOITER
Joseph H. Burchenal—MALIGNANT LYMPHOMAS AND LEUKEMIAS
Louis G. Welt—MANAGEMENT OF DEHYDRATION
G. Gordon McHardy—AMEBIASIS
John H. Talbott—GOUT
Carroll B. Larson—DIAGNOSIS OF LOW BACK PAIN
Joseph Rogers—DISORDERS OF MENSTRUATION

Systemic Fungous Infections

(THE "DEEP" MYCOSES)

J. WALTER WILSON

TABLE OF CONTENTS

J. Walter Wilson

received his A.B from the University of Southern California and M D from the University of California. Ten years in Medicine followed by 14 [illegible]

THE PAST TWO DECADES have witnessed a steadily decreasing incidence of most of the microbial diseases of man, especially with regard to those due to bacteria and spirochetes. In sharp contrast, human infections caused by fungi are becoming more prevalent. Although the study of mycology has become increasingly popular during this same period, there has as yet been no pronounced advancement in the methods of treatment for most fungous infections Herein [illegible]

killing the human host by becoming systemically disseminated. These are the so-called "deep" mycoses. Far from being the extreme rarities which they are generally considered, some of them affect thousands of persons annually, admittedly usually in milder, non-fatal forms, but always presenting the possibly more serious hazard to any individual. Some of these fungi appear to be gradually extending their activities beyond what was originally a rather sharply defined

geographic limitation, indicating the need for extensive epidemiologic study. Barring the discovery of some procedure which can break through nature's jealously guarded secret of limiting our allotted life span, the conquering of so many non-fungal fatal illnesses which the past half century has witnessed must inevitably leave more and more of us to succumb to fungi.

Despite the tremendous effort which has been devoted in the past to the study of immunology, this phase of many serious bacterial spirochetal, viral and protozoan microbial diseases is still not sufficiently well understood to furnish any practical methods of defense. Recent chemical and antibiotic victories in these fields have, in fact, lulled us into a degree of complacence which the future may well cause us to deplore. It is certainly not beyond the realm of possibility that strains of these microbes may eventually evolve which can resist all man-made chemicals and natural antibiotics. Indeed, [illegible] ing reg[illegible] sibility [illegible] as a "breathing spell" during which interim immunologic research should have been intensified.

This author believes that the deep mycoses have much to offer to the student of immunology. Each of these diseases exhibits one or more clinical syndromes, which differ from the others so much that at first glance they seem related solely because of their fungal origin. However, there are similarities, particularly some of recent discovery, which appear to be of more importance than the differences. When fully understood, these similarities may well furnish valuable clues for the study of basic immunologic processes, later transferable helpfully to bear upon non-fungal diseases In this regard, coccidioidomycosis has perhaps the most to offer, indeed, it has already blazed several interesting pathways. It is almost as protean in its manifestations as tuberculosis, yet it appears to behave immunologically in a much more easily understood manner. It also possesses a battery of testing procedures which seem correlative with studies of immunologic processes As our knowledge of the other systemic fungous infections grows, it appears ever more likely that they may all adhere fundamentally to this pattern.

It is for this reason that the order presented here was selected for the several deep mycoses · first coccidioidomycosis.

then sporotrichosis, followed by the others in a sequence which seems to this author to offer the best probability of understanding certain basic immunologic theories.

In the limited space provided here, much important information must be omitted. Intimate details of our knowledge of the history, mycology, pathology, laboratory and radiographic aspects of these disorders have undergone but little change recently and can be obtained when desired from any of several standard texts. Clinical photographs are similarly abundant. The present-day clinical and therapeutic aspects will be presented here, together with a framework of immunologic theory and practice.

COCCIDIOIDOMYCOSIS

(San Joaquin Valley Fever, Coccidioidal Granuloma)

In certain endemic localities wind-borne dust during the dry season carries spores of the fungus *Coccidioides immitis*. *Inhalation of this material results in a disease capable of* exhibiting a wide variety of clinical manifestations.

Although rarely encountered elsewhere, this disorder is worthy of study by all practitioners of medicine. Certain of its allergic and immunologic characteristics are so constant, well-defined and subject to informative correlation with its clinical course, that its investigation offers valuable clues which may lead to a better understanding of the discouragingly complicated immunology of other more prevalent and important granulomatous diseases. There is ample time for a person who has inhaled the fungus spores to travel to any other spot on the globe before symptoms appear. Correct identification of such a case is not difficult and will often spare the patient unnecessary or harmful therapeutic measures and usually afford much reassurance as to prognosis. Ability to recognize the disease in a non-endemic locality will also bring great credit among his colleagues to the diagnostician.

The most important endemic area is the San Joaquin River valley in south central California. Others have been defined in Los Angeles County, in Arizona, Nevada, New Mexico, Texas and the northern states of Mexico. There is also an endemic area in the Gran Chaco region in South America. Individuals of all ages seem equally likely to acquire the disease but it is encountered in its more serious phases pre-

dominantly in males in the third and fourth decades, in the more deeply pigmented races and in those whose occupations expose them to the inhalation of dust.

Transmission from living man to man has not been observed, although it is certainly possible; a mortician is known to have acquired a primary cutaneous infection from a cadaver. Wild rodents, cattle, dogs and sheep are frequently infected, but no authentic instances are known of the transmission of the disease to human beings from such sources.

Clinical Characteristics

Coccidioidomycosis resembles tuberculosis in many of its clinical manifestations, the principal differences lie in its strict avoidance of the intestinal tract and its failure to exhibit sarcoidal forms. It is necessary to differentiate sharply between the "primary" stage, which occurs frequently, and the "disseminated" or "granulomatous" type, which occasionally follows.

Primary pulmonary coccidioidomycosis.—Almost all previously uninfected individuals who inhale the fungus in a significant quantity acquire the disease. The incubation period is from 10 to 14 days. The "skin test," to be discussed in detail later, reveals an increasing percentage of positive reactors among those born into or moving into endemic regions for each year of their residence, in some regions reaching 90% within 3 or 4 years. More than half of these [illegible]

and physician to be "colds" or influenza. The remainder may exhibit pulmonary symptoms and signs of any degree, none of which is specific for this disease. Malaise, fever, chills, non-productive cough, night-sweats, nasopharyngitis, pleurisy and other chest pains, headaches and backaches are common symptoms.

A wide variety of pulmonary pathologic changes occur, including combinations of pleurisy, effusion, hilar thickening, parenchymal nodules, bronchopneumonia (or, at times, lobar consolidation), cavitation and miliary scattering. Signs revealed by auscultation and percussion tend to be less pronounced than the actual changes present would indicate

Pleuritic rubs, suppression of breath sounds, rales and dullness may be elicited.

Although x-ray examination is frequently negative even in well-developed cases, it may reveal a wide variety of combinations of abnormalities, most of which cannot be differentiated from those due to other pulmonary diseases. Other laboratory procedures are of little value in diagnosis or prognosis. Aside from the eosinophilia seen in association with the specific hypersensitivity mentioned in the next paragraph, the blood count and sedimentation rate are as would be expected in any acute pulmonary illness not of virus origin.

In from 6 to 16 days after the onset of symptoms, erythema nodosum (known colloquially as "the bumps" of "Valley Fever") or other typical forms of erythema multiforme (morbilliform, urticarial, bullous) develop in up to 30% of cases, more often in light-skinned individuals and in women. These eruptions are allergic in nature and are caused by the hematogenous dissemination to the skin of a toxic substance derived from the fungi in the active pulmonary [illegible]

[illegible] ally by the same mechanism. A significant degree of blood eosinophilia is commonly found in connection with this reaction. Patients who exhibit any of these phenomena are [illegible]

Almost all patients who acquire primary pulmonary coccidioidomycosis recover completely, without sequelae, except that they are apparently immune to reinfection for many years, probably for life. They retain for a similarly long period the ability to react to the skin test. In a small percentage, approximately one per thousand, the disease progresses into the disseminated, granulomatous form to be discussed presently.

Recovery may be delayed for some months in cases exhibiting extensive pneumonic infiltration, parenchymatous nodules or large cavities. Such patients must be carefully guarded against resuming activity prematurely, lest they lose

the chance of recovery. They should also be watched closely for evidence of dissemination.

Primary cutaneous coccidioidomycosis.—Although it was long believed that infection occurred frequently by direct inoculation of *Coccidioides* into the skin, this is probably extremely rare. It is true that a lesion in the skin is frequently the first manifestation of the existence of the disease, but the subsequent course of events in almost all reported cases strongly indicates that the fungus was brought to that point by being disseminated from a previously unrecognized primary pulmonary focus, a type which, it will be recalled, frequently remains subclinical.

Wilson, Smith and Plunkett observed a most instructive case, that of an embalmer who acquired the infection in an abrasion on his finger while embalming the body of a person whose organs were extensively involved. An indurated, almost painless chancre similar to that due to syphilis or sporotrichosis developed at the inoculated site, accompanied by a mild fever. Shortly thereafter, eight nodules appeared along the lymph channels draining this area, followed by epitrochlear and axillary lymphadenopathy, simulating sporotrichosis. The organisms were recovered from several [illegible]

[illegible] as large a percentage of cases as it is in the primary pulmo[illegible] most of [illegible] ne ski[illegible] gy probably were when first observed. One exception seems to be the case reported long ago by Guy and Jacob, which resulted from a puncture wound into the thumb by a cactus thorn A case recently reported by Trimble and Doucette was also typical.

Disseminated coccidioidomycosis, coccidioidal granuloma.—For reasons usually not clear, an occasional patient possessing primary pulmonary coccidioidomycosis fails to fight the disease immunologically. He sustains more and more pul[illegible] acquires other lesions by [illegible] the living organisms to [illegible] system or viscera. In striking contrast to the previously described benign primary

form, this type is fatal in perhaps 50% of instances.

Although the original inhalation of massive amounts of fungus spores cannot be excluded as a significant factor, the principal cause of dissemination seems to be the possession by certain individuals of an immunity mechanism which is inherently defective in some vital feature. Whether or not dissemination is to occur is apparently determined very early in the course of the infection, probably by an immunologic deficiency present even before it was acquired. Failure to recognize the primary infection and to guard the patient against premature overactivity may also play a part. Males are much more likely to sustain dissemination and to succumb, and the incidence increases proportionally with the depth of pigmentation in the skin. Filipinos resist the disease less well than much-darker-skinned negroes, however. (It will be worth recalling that the allergic "coccidioidids" considered to be so indicative of a good prognosis are encountered less frequently in man and in the more deeply pigmented races.)

Dissemination may occur early in the course of the disease and be rapid and massive, resulting in a multitude of small foci widely distributed throughout the body simulating miliary tuberculosis and leading to early death All degrees of dissemination in rate and extent are encountered between this picture and the other extreme, represented by a solitary disseminated lesion, developing long after the primary infection, and progressing slowly or even intermittently. Many such lesions eventually heal and some patients recover completely. In others, more foci develop [illegible]

[illegible]

are, in the order named, the lungs, skin and subcutaneous tissues, bones, joints, viscera, meninges and brain. The discovery of extra-pulmonary lesions indicates dissemination except in those extremely rare instances in which the skin furnished the portal of entry. In contrast to tuberculosis, the gastrointestinal tract is remarkably resistant to coccidioidal infection, both through the ingestion of the spores of the fungus and by hematogenous dissemination

Lesions in the viscera usually occur as part of a widespread dissemination and the clinical signs seldom point to one organ Meningitis is the most common central nervous

system form, and is almost always fatal, although occasionally slow in its progress. Light-skinned persons sustain dissemination less frequently, but when they do, meningitis is the predominant form. In all types, fever, chills, prostration, anorexia and progressive emaciation are typical symptoms

A hypochromic anemia is commonly encountered. The leukocyte count is variable. The sedimentation rate is usually maintained at a high level during the course of the disease.

Immunology

Even when it is so mild as to be entirely unmanifested clinically, the primary pulmonary infection apparently confers a complete immunity lasting for many years in all but one or two per thousand cases. Beginning after a week or two and accompanying this process is the development of hypersensitivity to the intracutaneous injection of an extract of cultures of *Coccidioides immitis* called "coccidioidin," prepared in the same manner as is "old tuberculin." Immediate flare (wheal) reactions are observed, of which the significance is not known. But the "delayed, tuberculin" type of response is highly significant. A rough quantitation of this reactivity is obtained by using 0.1 cc. of various dilutions (1:1,000, 1:100, 1:10) a few days apart, beginning with the weakest to prevent unduly severe reactions, especially when erythema nodosum or multiforme are present. *Clinicians have long* [illegible] *as a measure of* [illegible] *disease*, although [illegible] that the one dep[illegible] reactivity is retained for many years, perhaps for life.

Coccidioidin especially standardized for the purpose can be utilized as the antigen in a quantitative complement fixation reaction, as in the Kolmer modification of the Wassermann test. Positive reactions are not obtained for the first 2 or 3 months of the disease, *after that the quantitative "titer" thus determined serves the clinician as a measure of the severity of the infection and the extent to which it has spread* (or, in a later view, the total number of organisms actively engaged in producing the disease at that moment). Cure cannot be considered certain until it has subsided to negativity.

Using the interplay between the reaction to the skin and

complement fixation tests repeated at intervals of about a month, it is possible to make a much more accurate prognosis than by relying on any other combination of clinical observations, x-rays or other laboratory procedures. A highly positive skin test and negative complement fixation reactions indicate an excellent prognosis despite severe clinical illness; a negative reaction to the skin test and a high-titered response to the complement fixation means probable death by dissemination even when the patient appears entirely well by clinical examination

Positive reaction to a precipitin test using coccidioidin as the antigen can be obtained within a week or two and constitutes one of the earliest means of diagnosis. This reactivity disappears in a few months, however, without regard to the outcome of the disease, so that it has no prognostic value.

Coccidioidomycosis is unique in presenting useful reactions to such a battery of immunologic testing procedures.

Therapy

The *acute, primary pulmonary infection* remains subclinical in most cases and requires no treatment, in the remainder, all gradations of severity of pulmonary disease are encountered, for which appropriate, supportive, nonspecific medical and surgical measures should be selected on clinical grounds. To enhance the development of immunity, emphasis is placed on bed rest and adequate nutrition, in- [illegible]

knowledge frees them from implications of harmfulness. Antihistaminics may be utilized to relieve the symptoms of erythema nodosum or multiforme Cortisone and ACTH are contraindicated because of probable interference with resistance and immunity development

In *disseminated, granulomatous coccidioidomycosis* the [illegible] is the same as that for [illegible] [illegible] [illegible] [illegible] terally and treatment for anemia, including transfusions of whole blood, are indicated until fever ceases, the sedimenta-

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In *disseminated, granulomatous coccidioidomycosis* the management is the same as that for tuberculosis of similar degree, omitting the specific drug and antibiotic therapy and avoiding steroid compounds Absolute bed rest, a high caloric diet containing supplemental vitamins, liver extract parenterally and treatment for anemia, including transfusions of whole blood, are indicated until fever ceases, the sedimenta-

tion rate is normal and until rising skin test reactivity and lowering complement fixation titer indicate a favorable prognostic trend. Subsequent gradually increased activity may be allowed. It is dangerous to make this decision on clinical grounds alone. Surgical removal of all involved tissue has been employed frequently when the disease appeared to be sufficiently localized, such as in a single lung or lobe, or in an extremity. It cannot be denied that recovery has ensued in many instances. It is also apparent, however, that many of these patients would have recovered without surgery if the prognostic significance of the interplay between the intracutaneous and complement fixation tests as they were recorded had been analyzed. No method of therapy can be evaluated accurately without the ability to predict the prognosis to be expected if it is withheld.

The use of coccidioidin as commercially available has not proved advantageous and may be harmful. Specially prepared vaccines, unobtainable generally, were said by Jacobson and Stewart to be valuable. Several drugs and new antibiotics are under study; none has as yet been convincingly shown to be of specific value. A careful evaluation of all recent publications should precede any such experimental therapy.

Suggested Readings

[illegible] with respect to [illegible]lem [illegible] Pub [illegible]

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SPOROTRICHOSIS

From an exogenous source in nature exhibiting but little geographic limitation, human beings occasionally become inoculated with the pathogenic fungus *Sporotrichum schenckii*, usually percutaneously by means of a puncture wound. A syndrome develops which so closely resembles the primary stage of syphilis that it is termed "chancriform." Much more rarely, a generalized type of infection occurs. Correlation of this disease in its typical and atypical forms pathogenetically with other deep mycoses seems destined to yield considerable improvement in our understanding of mycotic infections in general.

The source of sporotrichosis in nature is usually vegetation, living or dead. Sporotrichosis has been reported from all areas of the globe where there is personnel capable of making the diagnosis In North America the northern portion of the Central States has the highest incidence; in Europe the majority of cases have occurred in France.

No age is exempt, and there seems to be no variation in susceptibility because of race There is a distinct predominance in males, however, and in the age groups between 20 and 50 years, almost certainly attributable in the largest part to the increased likelihood of the occupations of these individuals subjecting them to trauma by materials bearing the fungi.

Clinical Characteristics

Primary cutaneous sporotrichosis results from the inoculation of *Sporotrichum schenckii* directly into the skin Usually there is a history of a puncture wound or an abrasion, but penetration of intact hair follicles is considered probable in some instances. The incubation period is generally thought to be from 3 to 21 days, but it apparently may be delayed several months Most frequently the lesion first appears as an elevated pustule, pink or cyanotic in shade, frequently

oval in shape, with the long axis directed in line with the natural skin creases. There is no pain unless secondary bacterial infection is present. A small amount of pus can usually be expressed. This lesion slowly enlarges and forms an ulcer with a bright red base free of necrotic tissue, and with ragged undermined edges. Bleeding is easily induced. Small secondary papules usually surround the ulcer.

After a week or more, the majority of patients develop nodules along the draining lymphatic channels, small at first, but rapidly enlarging to form abscesses. Lymphatic vessels themselves are often reddened and indurated. Regional *lymph nodes become enlarged but usually do not* ulcerate. There is little tendency toward complete spon- [illegible]

As is pointed out in the appropriate chapters, this is the analogue of the type of infection which has been observed to result when *Coccidioides immitis* or *Blastomyces dermatitidis* was known to have been inoculated into the skin in exactly the same manner; such a reaction is also considered probable in histoplasmosis. This is not surprising in view of the similarity to the syndrome observed under the same circumstances in tuberculosis, yaws and American leishmaniasis. *Thus it appears that the route by which all of these* infections is acqured bears a profound relationship to the type of clinical syndrome which results. Whereas, at first glance, there seems to be a great deal of difference between the manifestations of sporotrichosis on the one hand and coccidioidomycosis, blastomycosis and histoplasmosis on the other, it appears likely that they actually resemble one another very closely provided only that they are acquired through the same portal of entry. *Coccidioides, Blastomyces* and *Histoplasma* form spores so easily dislodged from their sources in nature as to blow in the wind to be inhaled, by the same token, they do not adhere to vegetation and are seldom inoculated into the skin. Conversely, *Sporotrichum grows as a moist mat, closely adherent to its substrate vegetation,* hence it is seldom inhaled but frequently inoculated intracutaneously. The fact that each disease is seen almost exclusively in its predominant form, only occasionally duplicating the other type, is easily understood in the light of this concept.

Disseminated sporotrichosis is observed rarely, although it is likely that some such cases exist which are never correctly diagnosed. The majority of such instances were reported some time ago from France, where the incidence appears to have markedly decreased of late. The manner in which the infection was acquired has usually been obscure, but enough instances of involvement of mouth, pharynx or lungs have been observed to suggest that these routes are the likely ones. Again, the resemblance to coccidioidomycosis, blastomycosis and histoplasmosis when similarly acquired must be considered significant.

Especially worthy of emphasis is the fact that not a single case of such dissemination was encountered in the entire series of almost 3,000 cases studied in the South African mines, where the conditions were such that the intracutaneous route was almost certainly the only manner in which the infection was acquired. Neither can any other authentic case be discovered in the writings of other authors.

In its most common form, disseminated sporotrichosis begins as multiple subcutaneous firm nodules scattered over the body. These seldom ulcerate spontaneously, but become abscessed and, after incision or traumatic rupture, form chronic ulcers. From these the infection tends to spread to involve larger areas of the surrounding skin, simulating the lesions of tertiary syphilis, tuberculosis or other deep fungous infections. There is little tendency toward spontaneous cure and response to therapy is variable. Some cases progress rapidly to death, while others remain chronic for months. Associated with this syndrome (or even without it in some cases) there may be involvement of bones, joints, muscles, tendon sheaths, lungs, genitourinary system or other viscera.

Immunology

Subsequent to the recent reports indicating that when either *Coccidioides* or *Blastomyces dermatitidis* is inoculated intracutaneously a chancriform syndrome results which is comparable with the common form of sporotrichosis, it has become increasingly interesting to compare these diseases in other ways as well. If the immunologic reactions observed in these three infections are indeed closely parallel, an explanation is at hand for some of the heretofore "unreliable" results reported concerning the reactions to "sporotrichin."

Antigenic materials extracted from cultures of *S. schenckii* have been investigated, but not yet as extensively as in coccidioidomycosis.

Intracutaneous injection of sporotrichin has yielded variable results; de Beurmann interpreted a negative test as excluding sporotrichosis but found some "false positive" reactors, Du Toit stated that a positive reaction regularly occurs in patients with sporotrichosis; Gonzalez-Ochoa, Padilha-Gonçalves and Pontes de Carvalho agree. All these findings are consistent with experience in coccidioidomycosis except that it is now recognized that the "false positives" in that disease occur almost exclusively in persons who have had the infection and recovered, even though it was never perceptible clinically, perhaps this is the case in sporotrichin testing also.

The complement fixation test has also given variable results. Norden found it positive in only 2 of 11 cases, the titer not being stated. This is not surprising if this reaction adheres to the pattern which seems to be established in coccidioidomycosis and blastomycosis, and to be developing in histoplasmosis, in which the titer parallels the total quantity of involved tissues. In the cases of known *primary cutaneous blastomycosis* and *coccidioidomycosis* which have been recorded, the complement fixation test has also been negative or low in titer and transient. In *disseminated* cases of sporotrichosis, however, the titer might be expected to be high and the intracutaneous reaction weak or negative (anergic), in conformity with the poor prognosis, thus providing a situation in which a negative reaction to the skin test would not rule out the diagnosis of sporotrichosis.

Precipitin and agglutinin reactions have been reported, but their significance is not yet clear.

It is evident that much additional data will be needed before these tests can be evaluated. One pitfall which must be avoided is that of anticipating the *same* results from *all* these different procedures in a given patient at a given time, i.e., all tests negative or all tests positive. The tests do not parallel each other in coccidioidomycosis and it is evident that each reveals the presence of a different antibody, and that each is of different significance to the prognosis of the patient. It appears likely that similar conditions will be found to prevail in sporotrichosis.

It has long been known that potassium iodide is almost a specific drug in sporotrichosis, and nothing discovered recently seems destined to replace it, except in disseminated cases shown to have responded poorly to it. The dosage should be soon raised as high as can be tolerated, i e., up to 120 drops of the saturated aqueous solution daily in divided doses taken in the usual fashion with water or milk. The medication should be continued for at least a month after all signs and symptoms have disappeared. If the drug causes gastrointestinal disturbance, sodium iodide may be administered intravenously in somewhat reduced dosage (1-2 Gm daily). Half strength Lugol's compound solution of iodine is useful as a wet dressing for open lesions.

Surgery is contraindicated; aspiration of pus is recommended instead of incision and drainage. Moderately filtered x-radiation is helpful in resolving granulomatous tissue.

Vaccines prepared from cultures of the yeast phase have been suggested as supplements to iodide therapy when progress is slow, their status is questionable, as in other deep mycoses.

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NORTH AMERICAN BLASTOMYCOSIS
(Gilchrist's Disease)

The fungus *Blastomyces dermatitidis* causes in the human body a rare, chronic, suppurating granulomatous disease exhibiting two widely divergent clinical pictures. In one form, the skin alone is apparently involved during many years, without the general health of the patient being affected. In the other, the lungs are the primary focus, from which the disease as a rule soon becomes widely disseminated, usually causing death. When the term blastomycosis is used in the United States, without further modification, it is this disease which is designated.

North American blastomycosis is an appropriate name, since the disease is limited practically if not entirely to that continent. No age is exempt, but over half of the cases have occurred between the ages of 20 and 40. As is so common with the other deep mycoses, males outnumber females, in this instance almost 15 to 1. There is no apparent racial hypersusceptibility

Although it is obvious that infection with *B dermatitidis* occurs by acquiring the fungus from some exogenous source, the reservoir in nature has not as yet been discovered. The exact manner in which the fungus enters the body is also somewhat in doubt. Many cases undoubtedly originate in the lungs, most likely by the inhalation of dust containing spores Direct inoculation into the skin has long been considered of infrequent occurrence, but recent observations indicate the probability that this view should be revised, as will be discussed

CLINICAL CHARACTERISTICS

It has been customary to describe North American blastomycosis under the two clinical types which have been recognized for so many years, and named "cutaneous" and "disseminated." Recent developments would seem to warrant the different approach adopted here, admittedly perhaps prematurely, which utilizes four divisions primary cutaneous, primary pulmonary, chronic localized cutaneous and disseminated. It appears likely that the latter three classes overlap considerably and are perhaps but different manifestations of the same process.

Primary cutaneous blastomycosis.—Schwartz and Baum first advocated the view that the inoculation of *B. dermatitidis* directly into the skin of a previously uninfected individual did not result in the common chronic cutaneous form of the disease well known for so many years, but in a "chancriform" syndrome. They cited briefly 3 instances in which physicians had acquired the infection percutaneously and subsequently developed an ulcerative papule at the site of the inoculation, followed by regional lymphangitis and lymphadenopathy Wilson, Cawley, Weidman and Gilmer reported these cases in more detail, adding another, and emphasizing that this syndrome is logically acceptable as that to be expected from primary cutaneous inoculation, since it is almost exactly analagous to the clinical picture which results when the skin is directly inoculated for the first time with the organisms of tuberculosis, syphilis, American leishmaniasis, yaws, sporotrichosis and in the unique case of coccidioidomycosis reported earlier by Wilson, Smith and Plunkett. Certain immunologic phenomena to be discussed under that heading in later paragraphs were also considered to add credibility to this view

In these 4 cases the primary lesion appeared at the inoculation site as early as 1 week, followed in about 2 weeks by [illegible]

ency to be much milder than in its other forms All 4 patients recovered completely

Primary pulmonary blastomycosis —Although much evidence indicates that the lungs are frequently (if not indeed almost invariably) the portal of entry for blastomycosis, the ensuing disease is so insidious in its development that little is known of the early primary phases At first, it apparently resembles an ordinary subacute respiratory infection, presenting a non-productive cough, moderate fever, chest pain and dyspnea These symptoms gradually increase in severity, bloody and purulent sputum appears, and weakness, anorexia and weight loss are prominent. The fever increases and night sweats frequently occur. Death may occur without any evidence that the disease has extended beyond the lungs

Chronic localized cutaneous blastomycosis.—In its most common form, North American blastomycosis is first observed as a cutaneous lesion and remains apparently limited to the skin in that region throughout a chronic course extending over many years, rarely eventuating in spread to other organs. These facts have been widely accepted as indicating that the fungus was inoculated directly into the skin at the site of the initial lesion. It now seems likely, however, that this type of blastomycosis is but another of several forms which arise by dissemination from a primary focus in the lungs.

Regardless of arguments as to the mode of origin, localized cutaneous blastomycosis begins as an isolated papular lesion in or just beneath the skin, or as a subcutaneous nodule developing into an abscess and eventually rupturing to form an ulcer. The lesion soon develops a verrucous appearance studded with tiny pustules, the whole being raised about the surrounding normal skin from 3 to 6 mm. It slowly extends peripherally, and when some few centimeters in diameter begins to subside at the center where it eventually tends to "burn out," leaving atrophic noncontractile scars. Other lesions may appear, and by irregular peripheral growth and coalescence, gyrate, arciform and serpiginous forms are produced.

Expansion typically continues for many years, the infection eventually covering surprisingly large areas of the body

Disseminated blastomycosis—In addition to the specialized cutaneous form previously discussed, blastomycosis may be disseminated hematogenously to other parts of the body. The bones are involved in almost two thirds of the cases, most frequently the ribs and vertebrae.

The viscera are frequently invaded, especially the liver, spleen, prostate and kidneys Central nervous system lesions occur in about one third of the cases The intestinal tract is usually spared, in striking contrast to South American blastomycosis

There is usually leukocytosis with an increase in polymorphonuclears, and a heightened sedimentation rate. Anemia of the hypochromic type is typical.

As early as 15 years ago Martin called attention to the fact that persons whose sera were able to fix complement with blastomycin in fairly high dilutions (1:32) usually succumbed to the disease, while those whose sera were only slightly reactive or failed to react, recovered. Also, he noted that ability to react to the intracutaneous blastomycin test was a sign of a good prognosis, while those who died usually lacked this reactivity. Although by no means as clearly defined, this is the exact counterpart of observations made by many clinicians in coccidioidomycosis It must again be emphasized that there is insufficient evidence to conclude that immunologic resistance or susceptibility are intimately concerned with the substances responsible for these reactions, the clinician may nevertheless utilize them as valuable aids in prognosis.

It has been difficult, however, to explain why many patients exhibiting chronic cutaneous lesions over a period of years failed completely to react to the complement fixation test or did so only in low dilutions, while their skin test reactivity was frequently high. It is possible that some of the discrepancies may be resolved by the concept that the usual chronic, cutaneous form of blastomycosis does not result from primary percutaneous inoculation but by dissemination from a previously unrecognized primary pulmonary infection In this case, the lungs and other organs apparently succeed in resisting the disease, while the skin fails, although it tries hard and almost succeeds The histopathology of such cutaneous lesions is seen to represent a strenuous effort by the body to resist a very small number of blastomycetes by producing a tremendous cellular infiltrate and pseudoepitheliomatous hyperplasia This is in keeping with a high reactivity to the skin test and a low complement fixation titer

THERAPY

The treatment of North American blastomycosis has always presented many discouraging features Potassium iodide to the point of tolerance has been employed both orally and parenterally in most cases, with benefit in many and failure in others The same can be said of x-radiation, surgical intervention and vaccinotherapy Recently, the out-

look has improved considerably by Elson's discovery that certain derivatives of stilbene exert an apparently specific chemotherapeutic action on this disease. A large number of similar compounds, most of which contain the double bonded carbon of ethylene (styrene, nitrostyrene, cinnamic acid, etc.), are being investigated by Curtis *et al.*, and some appear promising. Stilbamidine is as yet the most widely used of these drugs and is administered in a dosage of 150 mg daily for 2 weeks, given slowly intravenously in 500 cc. of normal saline, followed by a second similar course after an interval of 2 weeks Neurotoxicity has been troublesome, especially [illegible] icity has [illegible] bamadine [illegible] is much better in the chronic cutaneous type than in the pulmonary or disseminated forms. The status of this type of chemotherapy is in a state of flux at the time of this writing, and more recent publications should be sought before treatment is begun.

In the localized, chronic cutaneous form, the diseased areas may be healed by thorough curettage and desiccation, a procedure which is accomplished with surprising ease since all involved tissue separates without resistance from an apparently comparatively healthy base. Subsequent use of Lugol's compound solution of iodine diluted equally with water as a daily dressing usually results in healing by scarring. Recurrences are fairly common but usually yield to subsequent retreatment while still small Attempts to remove large areas of involved skin surgically, followed by full thickness grafts, have been less successful. The recent concept that this form of the disease really represents the end stage of a process of dissemination in which all body tissues except the skin have acquired sufficient resistance against it, removes to a large extent the reluctance to attack such lesions surgically because of fear of disseminating the organisms.

In the pulmonary and disseminated forms particularly, it is necessary to employ all those measures which are calculated to enhance the development of immunologic resistance, such as prolonged rest in bed, a high caloric and high protein diet, supplemental vitamins (especially B and C), crude liver extract and transfusions of whole blood A heat-killed

vaccine prepared from cultures of *B. dermatitidis* in the yeastlike phase is recomm...
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consid ... been accomplished. Further details of these procedures may be obtained from the writings of Martin and Conant *et al*

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HISTOPLASMOSIS

(Reticuloendothelial Cytomycosis)

The fungus *Histoplasma capsulatum* causes histoplas sis, usually described as a rare, chronic, fatal, granuloma disease with a distinct predilection for the reticuloendoth system. During recent years, however, increasing evide indicates the probability that in certain geographic areas infection, instead of being rare, occurs frequently. In tl instances it takes the form of a pulmonary disorder so n as to result almost uniformly in recovery without its fung nature being recognized but nevertheless conferring sul quent immunity to reinfection. All practitioners of medic should, *therefore, now become familiar with the essen* facts concerning its diagnosis so that it will be less freque missed. Statistical studies may then clarify its epidemiolc pathogenesis and immunology.

Histoplasmosis occurs most frequently in North Ameri concentrating in the region of the Mississippi River vall A significant numl [illegible] America, Central [illegible] islands and South [illegible] several European countries Greater awareness of the dise may bring additional cases to light in these and other ar to confirm the extensive distribution which seems indicat [illegible] hood, when the trend is much less pronounced. The influen of occupation, so impressive in other deep mycoses, seer relatively unimportant here, although persons whose wo brings them into intimate contact with the soil appear mo likely to become infected.

Emmons first demonstrated the presence of *Histoplasm capsulatum in soil in 1949, confirmation was rapidly add* by several observers.

The principal portals of entry for the infection are appa ently the respiratory and gastrointestinal tracts, althoug "primary" cutaneous and mucosal lesions have been d scribed. The exact manner in which the fungus is brought t the body is in doubt, but there is mounting evidence that th principal route may be by the inhalation of the organism

with air-borne dust in the manner in which coccidioidomycosis is almost invariably acquired.

CLINICAL CHARACTERISTICS

Although the proof cannot yet be said to be conclusive, it is virtually certain that histoplasmosis occurs in two widely divergent forms: a mild primary infection affecting a large percentage of exposed individuals and a severe disseminated type encountered only rarely. There is apparently close resemblance to coccidioidomycosis in many respects, especially with regard to epidemiology and immunity, although the two diseases differ extensively in their pathology.

Primary pulmonary histoplasmosis.—The exact status of this entity has not as yet been conclusively established. A brief résumé of the evidence for its existence is as follows.

It has long been known that many persons exhibit roentgenologic evidence of pulmonary calcification which cannot be attributed to tuberculosis or any other disease heretofore delineated. Sometimes the spleen is similarly involved. The incidence of this phenomenon increases with advancing age from childhood to early adult life and is higher in certain geographic regions in a manner highly suggestive of its being due to some environmental cause. The discovery that it could be statistically correlated with reactivity to the intracutaneous injection of a substance known as "histoplasmin," analogous to tuberculin and coccidioidin, makes it appear likely that it is frequently the result of infection with *Histoplasma capsulatum*. It is only necessary to accept the view that the active phase of the disease can be frequently so mild as to be asymptomatic, or, when more severe, that it is incorrectly attributed to "the common cold," "influenza," tuberculosis, bronchopneumonia or other entities. The situation seems to be identical with that which has been thoroughly established in coccidioidomycosis, and to students of the latter disease further evidence appears to be unnecessary. In this stage, it is difficult to recover the fungus in culture or to identify the presence by microscopic examination. Correct diagnosis is most easily made by observing a "conversion" of the patient's skin reactivity to "histoplasmin" from negative to positive during the early weeks (see below).

Extra-pulmonary primary histoplasmosis.—The existence of this type of infection is much more doubtful than the pul-

monary form. The disease has been produced in animals, however, by direct inoculation into the mucosa or skin, and similar infection of human beings must be considered possible. Curtis and Harrell have reported a case exhibiting a chancriform lesion of the penis, which they believe to have been intracutaneously acquired.

Dissemin[illegible] apparently [illegible] it is in the [illegible] mosis was first recognized and subsequently accurately delineated. About 150 cases have been recorded up to the present time. Although not as yet proved, it is likely that disseminated cases simply represent those few instances in which persons afflicted with the primary form fail to resist the disease immunologically in the usual completely satisfactory manner, as is the case in coccidioidomycosis. In partial confirmation it may be pointed out that no alternative mechanism has as yet been plausibly demonstrated in almost 50 years of study.

The reticuloendothelial system is particularly vulnerable to invasion by *Histoplasma capsulatum*, but eventually almost any tissue in the body except the cortex of bone or cartilage may become involved. There is much variation in the rate of progress of the disease, and the clinical picture is protean. It is usually that of a subacute to chronic, wasting, irregularly febrile disease, accompanied by anemia, leukopenia, lymphadenopathy and enlargement of the spleen and liver. Anorexia, nausea, vomiting, diarrhea and gastrointestinal discomfort may be prominent symptoms, pleurisy, pulmonary infiltration and tracheobronchitis are frequently in evidence; endocarditis, involvement of the adrenals, or central nervous system invasion may occur. Mucosal lesions are often present, especially involving the genitalia and the mouth and tongue, these are usually torpid ulcers surrounded by induration. Similar ulcers may occur in the skin, and purpuric or bullous eruptions are occasionally seen. This form of the disease is almost always fatal, rapidly in children, more slowly in adults.

IMMUNOLOGY

The present trend indicates that histoplasmosis probably is acquired by large numbers of persons, remaining mild

while conferring a lasting immunity in all but a few. As in coccidioidomycosis, it is believed that the small percentage of individuals who develop the fatal disseminated form do so because of the possession of some inherent defect in immunologic mechanisms In coccidioidomycosis there is as yet no clue as to the nature of this defect, but it has been repeatedly pointed out that disseminated histoplasmosis is frequently associated with other diseases of the reticuloendothelial system such as leukemia, lymphosarcoma or Hodgkin's disease. A logical explanation is that the lymphoblastomatous process causes the reticuloendothelial system to fail in the performance of one of its most important postulated duties, the production of some "specific antibody" necessary for the development of immunity. It is possible, although unlikely, that the reverse is true and that histoplasmosis may actually be the cause of some cases of the clinical syndromes called lymphoblastoma. It has also been noted that histoplasmosis is associated with other granulomatous disorders, especially tuberculosis, more often than coincidence would indicate This is also the case with other deep mycoses, suggesting that the immunologic defect can be polyvalent.

At the present time, due to lack of adequate material for pathologic studies, investigations in histoplasmosis are heavily dependent on the reactions obtained to an antigenic substance, histoplasmin, which is extracted from cultures of *Histoplasma capsulatum* in a manner identical to that employed in the manufacture of old tuberculin and coccidioidin

During each of the past few years more and more evidence has been accumulated to indicate that the serologic, allergic and immunologic phenomena associated with histoplasmosis closely resemble those of coccidioidomycosis, a surprising fact in view of the differences in the pathologic propensities of the two fungi The facts concerning these features are much more firmly established in coccidioidomycosis, largely because they began to be intensively studied some 12 years earlier; valuable clues derived thereby are accelerating progress in the study of histoplasmosis

Histoplasmin has been most extensively studied when employed as an intracutaneous test, using 0 1 cc of a 1 1,000 or 1·100 dilution Immediate wheal reactions have been observed, but their significance is not known The delayed, tuberculin type of response, consisting of an erythematous

papule at least 5 mm. in diameter in 48 hours is considered positive. In many parts of the world, large groups of persons have now been tested in this manner, including significant numbers of representatives of all age groups and of those apparently free of all disease as well as those suspected or known to be harboring histoplasmosis. The percentage of positive reactors encountered varies tremendously in different geographic locations, from practically zero to almost 80%; *furthermore, the incidence increases sharply at each step in* the age groups from infancy to adult life. In the light of knowledge of tuberculin and coccidioidin reactions, these facts can be explained only by concluding that positive reactors to histoplasmin either are, or have been previously, infected with histoplasmosis. Many of those reacting positively to histoplasmin recall no significant illness. They show evidence of pulmonary calcification previously unexplainable but now logically attributable to the benign form of histoplasmosis. Although not proved, it may be useful for the clinician to assume that a positive reaction to the histoplasmin test *quantitatively parallels the specific immunity to reinfection, as is thought to be the case in coccidioidomycosis* Such reactivity apparently may last for many years.

The complement fixation reaction, using especially standardized histoplasmin as the antigen, is being actively investigated at this time. While its status is not as yet well clarified and some reservations must be held with regard to specificity, it seems likely that the titer can be correlated with the severity and extent of the disease present at the time the test is performed, again paralleling experience with coccidioidin.

Thus, interplay between the degree of response to the intracutaneous test (indicating immunologic resistance) and the complement fixation test titer (indicating the extent and severity of the disease which is present) may prove of value in prognosis as it does in coccidioidomycosis.

[illegible] histoplas- [illegible] one of the most [illegible] next few years [illegible] its importance. It is also to be hoped that it has much to contribute to the better understanding of immunologic processes in general

Therapy

The acute, primary pulmonary form is too poorly recognized and understood to have afforded any guides for treatment In the vast majority of instances it remains subclinical and requires no therapy, when more severe, non-specific supportive medical and surgical procedures should be selected on clinical grounds. Bed rest, adequate nutrition and supplemental vitamins, principally of the B complex series, will probably enhance resistance and the development of immunity. Antibiotics of fungal origin may be harmful, and therefore should be withheld unless there is evidence of concomitant bacterial disease for which they are specifically indicated Cortisone and ACTH are probably contraindicated because of interference with resistance and immunity development.

There is as yet no specific therapy for disseminated, granulomatous histoplasmosis Favorable results have been attributed to sulfonamides. More recently, ethyl vanillate has been reported of benefit in a series of several cases At this time, the disease is being so extensively studied that better therapeutic methods are almost certain to be forthcoming in the near future A review of the most recent literature is therefore mandatory before treatment is outlined

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ACTINOMYCOSIS

(Lumpy Jaw, Nocardiosis, Maduromycosis, Madura Foot)

The *Actinomycetes*, a large group of primitive fungi closely allied to bacteria, contains a few species pathogenic to man and animals. They cause actinomycosis, a chronic granulomatous suppurative disease usually characterized by intense induration, followed by the evolution of deep abscesses which eventually rupture and leave persistent multiple draining sinuses. In addition to this typical picture, however, actinomycosis is capable of such wide variations in its pathogenicity that it cannot be ignored in differential diagnosis by any practitioner of medicine, even in the narrower specialties

Actinomycosis most frequently results from infection by a single species of fungus, *Actinomyces bovis*, the only pathogenic fungus which prefers to grow anaerobically. Certain other forms, closely allied morphologically but differing by growing only aerobically, are capable of causing the same types of clinical disease, these were formerly included within the genus *Actinomyces*, but are now usually accorded a separate generic name, *Nocardia*

Actinomycosis occurs in all parts of the world—as Cope so aptly stated, "wherever there is a microscope and a laboratory" to ascertain the diagnosis Of all the deep mycoses it is the most frequently encountered. No age is exempt, but the incidence is higher in the third and fourth decades of life Two thirds of those affected are males.

Actinomyces bovis has been isolated from normal mouths and throats, it is probably often present in these locations and in the gastrointestinal tract of most healthy human beings and animals. When such an organism, usually existing as a harmless saprophyte, succeeds in causing disease, the infection is said to be endogenously acquired, staphylococci and streptococci are more familiar examples. It is extremely important

to study the contributory factors by which such usually innocuous organisms become endowed with pathogenic powers because measures directed toward the control of such factors may be more effective therapeutically than those antagonistic to the microbes themselves. In the case of actinomycosis, trauma, which presents the fungus with devitalized tissue far enough from the surface of the body to furnish the necessary anaerobicity, is the most important of these factors. Thus, the onset of the disease frequently follows the extraction of infected teeth, fractures (especially of the jaws) and bites or other injuries inflicted by the teeth of human beings or animals.

The presence of disease due to other causes may also serve in a similar manner by lowering tissue resistance to the *Actinomyces*. Another important factor, and one of great significance when therapy is considered, is that a symbiotic alliance seems to be established between *Actinomyces bovis* and endogenous bacteria, the combination exhibiting a degree of pathogenicity not possessed by either ally alone. It is significant in this regard that actinomycosis is never completely reproduced in animals experimentally inoculated with *Actinomyces bovis* in the absence of trauma or concomitant bacterial infection. These facts explain the universal distribution of actinomycosis of the anaerobic type, since wherever man exists he carries with him endogenous organisms capable of producing the disease when the proper opportunity is offered.

The similarly wide distribution of the disease when caused by the aerobic *Nocardiae* must be explained differently, since they have not been found in healthy individuals. Pathogenic strains have, however, been recovered from the soil, where they are apparently widely distributed along with multitudinous species of the ubiquitous soil-fungi, belonging to the genus *Streptomyces*, which they closely resemble. It is significant that in the majority of instances infection with these organisms has involved either the lungs, due to inhalation of dust, or the feet, due to direct inoculation of soil into wounds.

Clinical Characteristics

Actinomycosis occurs in several well defined clinical forms. In over half the cases, involvement occurs in the region of

the face or neck and is termed the "cervicofacial" type. The abdomen is the site in about 20% and the chest in 15%. In the small remainder of instances the disease selects other portions of the body such as the extremities, skin, bones, joints, kidneys, ovaries, liver or central nervous system Frequently, however, it is evident that such lesions have arisen by dissemination from a focus of one of the three more common types.

Cervicofacial actinomycosis.—It is fortunate that this, the commonest form of the disease, has the best prognosis. The portal of entry is the mucous membrane of the mouth or pharynx, the tonsils or the region around the gums and teeth.

After a short time during which the infection reveals no special differentiating features, the overlying skin assumes a dark red or cyanotic hue; induration develops of such firmness as to have inspired the term "ligneous (woody) phlegmon," causing marked limitation of motion and muscular spasm in the vicinity. The surface becomes irregular, abscesses develop slowly and periodically, finally rupture or are incised, leaving sinus tracts which persist for months, draining serosanguinous, purulent fluid. This exudate may contain tiny, yellowish, friable masses of the fungi called "sulfur granules," to be described later in detail Healing occurs only very slowly by cicatrization. Usually lesions in [illegible] be- [illegible] ng. [illegible] he [illegible] he patient is little affected.

Abdominal actinomycosis.—In this form, invasion of the tissues usually occurs by way of the appendix or cecum, occasionally, the fallopian tubes, gallbladder, stomach or liver appears to be the primary site It must be recalled that the fungi are present in the entire intestinal tract of many normal persons, where they are carried from the mouth by swallowed saliva Trauma is not so apparent here as a contributory cause for pathogenicity as in the cervicofacial type, but bacterial infection is undoubtedly important.

The symptoms are often vaguely those of chronic appendicitis, salpingitis or cholecystitis, occasionally cystitis or pyelonephritis; sometimes the picture of malignancy is simulated Indistinct masses may be palpable. Laparotomy is,

usually necessary to clarify the diagnosis, although occasionally abscesses rupture spontaneously through the abdominal wall or elsewhere and produce the draining sinuses so typical of actinomycosis, yielding pus, perhaps with diagnostic granules.

Thoracic actinomycosis.—Primary pulmonary infection results from the aspiration of material derived from the mouth containing *Actinomyces bovis* The aerobic *Nocardia* may be inhaled with dust. In early stages, the infection cannot be differentiated from other subacute or chronic pulmonary diseases, a valuable differential sign is the early appearance of expectorated pus, sometimes bloody, indicating the development of abscesses. With or without pleuritic pain or pleural effusion, the disease may penetrate to the exterior through the chest wall, presenting then the appearance described for the cervicofacial type. Progressive wasting, dyspnea, fever, noctidrosis and anemia usually occur

Maduromycosis, mycetoma, or madura foot—These terms have been applied to rare, chronic, deep infections of the extremities caused by a wide variety of fungi. The disease in general conforms to the previous description of classic actinomycosis and in North America is usually identical, being caused by the same two genera of fungi, *Actinomyces* and *Nocardia*

Other forms of actinomycosis—Actinomycosis may produce a wide variety of signs and symptoms by invading almost any part of the body, either by direct extension or hematogenous dissemination.

Immunology

The allergic and immunologic phases of actinomycosis have been extensively studied, but the reactions are not consistent and cannot be accurately correlated with its clinical course. Some of the discrepancies may be due to difficulty in the production of reliably uniform antigens or suspensions of the organisms. It is also probable that considerable clarification could be obtained if the theories of the observers were adapted to comply with the results of the tests, rather than allowing such discrepancies to cause the abandonment of the procedures as "useless."

Hypersensitivity has been demonstrated during actinomycosis by the response to the intracutaneous injection of cul-

ture filtrates; both local and systemic reactions occur. The significance of this reactivity is in doubt.

Complement fixing antibodies as well as agglutinins and precipitins have been demonstrated in the sera of persons infected with actinomycosis, but not consistently or with enough specificity to warrant the use of such procedures for diagnostic or prognostic purposes.

It is worth pointing out that it is possible that these discrepancies are actually due to attempts to fit the results of the tests into the observer's preconceived ideas of their significance, rather than allowing them to speak for themselves. Perhaps the precipitin and complement fixation tests actually should be interpreted as they are in coccidioidomycosis, in which disease they appeared to be equally irregular until better interpretation revealed them to be consistently valuable. Also, there is a wide variation in the antigens as prepared by different observers, and some uniformity will be necessary before the subject can be clarified.

Therapy

There is no doubt that the advent of the sulfonamides and the antibiotics has bettered the prognosis of actinomycosis markedly, but none of these alone nor any combination of them should be considered as specifically curative without adjunctive therapy. Initially, a dramatic degree of improvement follows such treatment, but soon a point is reached where further progress is extremely slow even though adequate dosage is continu [illegible] of such medication is [illegible] and its readministratio[illegible] *indicate that it is capable of holding the activities of the* fungus in check. It seems more likely, however, that the majority, if not all, of the effect of the substances should be attributed to their ability to combat bacterial infection and thus deprive the fungus of the symbiotic alliance which has been previously alluded to as one of the principal reasons for its acquisition of pathogenicity It is true that in vitro certain strains of *Actinomyces bovis* seem susceptible to one or another drug, but it must be recalled that cultures of this organism are not easily obtained or maintained in vitro even without such antagonistic substances Selection of medicaments by such "specific testing" is permissible, but it is even

more important to investigate in the same manner the bacterial flora which is also present and administer the appropriate drugs to combat this factor as well. Nocardiosis apparently responds better to sulfonamides than to antibiotics, the reverse characterizes *Actinomyces bovis* infections. *Neither form of chemotherapy helps the other forms* of maduromycosis appreciably. Isoniazid has been recommended for *A. bovis* infections by McVay and Sprunt. Gonzalez Ochoa recommends 4,4-diamino diaphenyl sulfone for disease caused by *N. brasiliensis*

Vaccine therapy has been advocated by several workers, [illegible] inves- [illegible] actu- [illegible]

After the initial amelioration is obtained by "specific drugs," surgical drainage should be adequate, and all tissue *manifestly* beyond recovery should be debrided. *Intelligent* use of antibiotics permits the surgeon more latitude in his procedures.

In treatment of the chronic, low grade disease which remains after the above procedures have been carried out, drugs seem of little value. Iodides may be used in maximal dosage, either orally, if tolerated, or intravenously Heavily filtered x-radiation or radium implantation is of great value, especially in the cervicofacial type.

It is extremely important to point out that the factor responsible for the ultimate complete eradication of the disease is almost certainly the body's natural ability to resist and heal the infection, whether this be by the development of specific immunity, phagocytosis or some other mechanism Prolonged rest in bed with adequate nutrition and multiple vitamin supplements, especially of the B complex series, are vital

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[illegible] agnosing [illegible] enferm

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SOUTH AMERICAN BLASTOMYCOSIS

(Paracoccidioidomycosis)

South American blastomycosis is a chronic, progressive, [illegible] the most common of which are *Blastomyces* (or *Paracoccidioides*) *brasiliensis* Although the infection occurs in only a small portion of the world, facts concerning its pathogenesis are worthy of study by practitioners in other regions as well, lest the search for methods of control of the medical mycoses in general be hampered by lack of information concerning some feature less elusive in this entity than in others. In addition, there are two instances in which the diagnosis has been made outside the confines of South America, although in both cases it seems likely that the disease was originally acquired there.

The incidence of the disease is highest in the ages from 20 to 50, and males outnumber females 6 to 1. There is a remarkably high incidence among agricultural workers, pre-

sumably because they come into more direct contact with vegetative material.

The habitat of the causative organism in nature has not yet been established Clinical aspects of the disease indicate strongly that the portal of entry is usually the oral mucosa. Prevalence of the infection among agricultural workers is generally accepted as being due to their habit of cleaning the teeth with small fragments of wood and chewing the stems and leaves of various plants

Clinical Characteristics

The primary lesion of South American blastomycosis almost always occurs in the mucous membrane of the gastrointestinal tract, usually that of the mouth, occasionally that of the tonsils, larynx, nose, eye, intestine or anus. Rarely, the lungs appear to be the primary site. Primary inoculation into the skin is apparently rare, and convincing evidence is difficult to obtain

From any of these primary foci the infection may be disseminated by both the lymphatic and hematogenous routes and may affect practically all organs eventually.

Involvement of the lymph nodes, sooner or later in the disease, is one of the most common features of South American blastomycosis The cervical and the submaxillary groups are most commonly affected. Until recently, pulmonary involvement in South American blastomycosis was considered to be sufficiently rare as to furnish a means of clinical differentiation between that mycosis and North American blastomycosis (Gilchrist's disease). Many authors have shown, however, that the lungs are affected in a high percentage of cases (57 to 94%). The mouth and pharynx are affected in almost every case, the gastrointestinal tract less frequently, and usually only secondarily to other manifestations of the disease. Appendiceal lesions have been studied by several authors Involvement of the anorectal region has been reported The spleen and liver may be enlarged. Peritoneal localization has been reported. Involvement of many other organs has been observed occasionally, producing highly variable clinical pictures.

Jorge Lobo first observed and described a keloidal type of cutaneous involvement especially affecting the back and legs It bears no resemblance to the usual clinical picture of the

disease and is thought by some to be due to a different fungus.

Immunology

There seems to be little attempt on the part of the human body to resist the progress of South American blastomycosis by specific immunologic methods.

Intracutaneous Test

Intradermal injection of antigens prepared from cultures [illegible] *yielded uniform results* [illegible] The test does not seem [illegible] tigens. Almeida, Lacaz and Cunha consider it of value in both diagnosis and prognosis. In severe forms of the disease, reaction is negative.

Complement Fixation Reaction

Standardization of this reaction has not yet been achieved, and its significance is not known. There are indications, however, that a high titer indicates a poor prognosis and that recovery may be heralded by a decreasing titer (Lacaz and Fava Netto). (See Coccidioidomycosis, North American blastomycosis and histoplasmosis.)

Therapy

Iodides, gold and antimony salts and antiseptic dyes are considered valueless Sometimes localized lesions may be successfully destroyed by electrocoagulation. Almeida reported good results with specific vaccines.

Sulfadiazine is the drug most extensively used in practice, fractionally administered in a total dose of 2 to 4 Gm. daily. Clinical improvement may be expected in most patients and clinical cure occasionally. Relapses are frequent when the drug is discontinued, but sufficiently prolonged administration may be prevented by toxic manifestations. As with the other deep mycoses, rest, a diet high in protein content and those vitamins which are related to immunity development (vitamins B and C) should be maintained

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CRYPTOCOCCOSIS

(*Torulosis; Busse-Buschke's Disease, European Blastomycosis*)

A yeastlike fungus, *Cryptococcus neoformans*, which apparently is widely distributed in nature, occasionally causes a human infection called cryptococcosis or torulosis, a chronic wasting, highly fatal disease characterized by a pronounced predilection for involvement of the central nervous system Probably of more frequent occurrence than the literature indicates, many cases are unrecognized because of lack of familiarity with the infection's clinical manifestations and details of its mycologic diagnosis.

Cryptococcosis has been reported from all continents and does not appear to be limited by geographic factors, in this regard it resembles actinomycosis and differs from the other deep mycoses. This tends to confirm the view that the infection is frequently endogenously acquired and/or that the organisms are widely dispersed in nature It also suggests that the factors which determine whether or not infection takes place are peculiar to the individual host rather than to the fungus

Cryptococcosis occurs in all decades of life, but predominantly between the ages of 40 and 60 Males are affected about twice as frequently as females There is no apparent variation in susceptibility because of race or occupation.

Benham found that a number of strains of Cryptococcus isolated from various sources in nature differed morphologi-

cally, culturally and serologically from several recovered from normal human skin, but that some of the latter could not be distinguished from specimens derived from fatal cases of cryptococcosis. Emmons has isolated from soil 4 strains of *C. neoformans* which were pathogenic for laboratory animals. Fermenting fruit juices have yielded similar pathogenic [illegible]

as yet been traced conclusively to any of these sources, but it appears likely that strains of *C. neoformans* capable of pathogenicity are frequently present on the skin and mucous membranes of normal individuals, awaiting the fortuitous combination of circumstances which allows infection to occur. Factors of trauma and symbiotic alliance with bacteria which are so important in the often predominantly endogenous deep fungous infection, actinomycosis, are not apparently operative in cryptococcosis. There is, however, a resemblance to histoplasmosis, for cryptococcosis is associated with lymphoblastomata more frequently than can be explained by coincidence, principally Hodgkin's disease and the leukemias.

Although cryptococcosis occurs in animals by natural means, there has been no reported instance of human infection derived from them. Direct transmission from man to man has not been proved, although Cox and Tolhurst considered it not unlikely after discovering the organisms in the sputum in 4 cases.

The route by which the fungus enters the body is obscure. Freeman, reviewing the literature in 1931, believed it most likely that the usual portal of entry is the lungs In 1946 this view received strong support from Cox and Tolhurst, who demonstrated that the fungus could resist drying for at least 10 months and hence could be inhaled with dust. A history of a preceding respiratory infection can be obtained with statistically significant frequency from patients suffering from any form of cryptococcosis

Infection by direct inoculation through the skin or mucous membrane has been accepted as the portal of entry by many authors when reporting cases, but in most instances features are cited which cast doubt on the validity of such an assumption The portal of entry has occasionally been shown to be the oropharyngeal or gastrointestinal tract.

C neoformans has been cultured from the blood of infected

persons, indicating that the disease may be hematogenously disseminated. Lymphatic spread occurs in laboratory animals but has not been proved in human disease. Semerak suggested that meningitis might occur by direct spread of the organisms from the nasopharynx.

Clinical Characteristics

Although cryptococcosis is best known because of its predilection for concentrating in the central nervous system, such involvement is often absent. The lungs are almost as frequently affected, perhaps even more so, and, since they probably afford the portal of entry in most instances, it is fitting that the pulmonary form of the disease be discussed first. Involvement of bones, skin, mucous membranes and viscera will be covered in later paragraphs.

Pulmonary cryptococcosis —The clinical picture of pulmonary cryptococcosis cannot be differentiated from other chronic lung infections, except perhaps by its tendency to produce fewer symptoms than the extent of pathology demonstrated by physical signs or by radiography would indicate There have been no observations which would suggest that a "primary" form could be differentiated from a "disseminated" type in the absence of proved extrapulmonary lesions A mild degree of fever is frequently exhibited, though by no means consistently, cough is sometimes present, and sputum is rather infrequently produced There is occasional pleural pain and, rarely, effusion Physical signs usually indicate bronchitis or pulmonary consolidation, dullness and diminished breath sounds are commonly elicited, but rales or rhonchi are rare, since exudation is not common

In some cases the pulmonary involvement increases sufficiently to cause death, more frequently, the infection is disseminated to the central nervous system or other organs Some cases of pulmonary cryptococcosis have resulted in recovery, leading Stoddard and Cutler, Sheppe and other authors to conclude that there is considerable tendency toward healing in the pulmonary form Since cryptococcosis is seldom suspected as the diagnosis of lung disease in the absence of extrapulmonary lesions, it is entirely possible that it actually occurs frequently and heals without recognition, as is known to be the case with some other deep mycoses (see coccidioidomycosis and histoplasmosis)

Central nervous system cryptococcosis.—Signs and symptoms indicating invasion of the central nervous system are referable either to meningitis or increased [illegible] sure. The e [illegible] and fronta [illegible] sistent and [illegible] violent, accompanied by projectile vomiting, at times suggesting subarachnoid hemorrhage. Vertigo, dizziness and neck rigidity soon appear. Amblyopia occurs often, and nystagmus diplopia and ptosis occasionally appear. Severe mental aberrations are common, such as restlessness, irritability, disorientation and hallucinations, alternating with periods of depression and loss of affect; sometimes a definite psychosis may be closely simulated, especially if the appearance of the characteristic headache is delayed. Epilepsy has occasionally been observed.

Focal lesions of the brain and occasionally of the spinal cord occur, and may lead to the diagnosis of tumor if the more generalized symptoms are absent or mild; cryptococcosis has been occasionally diagnosed from material obtained during operations performed for the removal of "tumors." Such focal lesions may occur anywhere in the central nervous system. Resulting signs and symptoms will accordingly be so variable as to preclude discussion here, conforming to ordinary neurologic topographic diagnosis. Ataxia and hemiplegia are the most common presenting features.

Cryptococcic meningitis or meningo-encephalitis may or may not be accompanied by a usually mild and irregular fever. The pulse rate is less likely to be elevated by fever than depressed by the increased intracranial pressure. The other usual signs of increased intracranial pressure are common. Examination of the cerebrospinal fluid will frequently prove the diagnosis. The pressure is increased, the fluid usually yellowish or otherwise discolored, the cell count raised and predominantly lymphocytic, the protein increased, and the chlorides and sugar significantly diminished. The colloidal gold curve may be normal or of the meningitic type. Characteristic singly budding cells of *C neoformans* can often be seen by direct microscopic examination of centrifuged specimens or the fungus recovered in culture. Without this careful laboratory confirmation of the causative organism, the entire picture is consistent with tuberculous menin-

gitis, and this diagnosis has undoubtedly been erroneously made on many occasions.

Although there may be short remissions, the disease progresses slowly to death, usually in 3 or 4 months, sometimes only after 1 or more years. Recovery has not occurred in any case in which the diagnosis was established. However, it is entirely possible, and even considered likely by some authors, that many cases of mild infection may occur and recovery ensue without the disease being recognized.

Cryptococcosis in other organs.—In about one fifth of the cases of cryptococcosis there is associated enlargement of the lymph nodes, spleen or liver. Frequently this apparently is entirely unrelated to the infection and presents the picture of Hodgkin's disease or another lymphoblastomatous disorder. First noted by Fitchett and Weidman, this phenomenon has since been emphasized by many authors until there is no longer any doubt that it occurs more frequently than can be accounted for by coincidence (approximately 10%). The correct interpretation of this relationship is not yet clear. It may be that cryptococcosis actually causes Hodgkin's disease (or an indistinguishable syndrome) in some cases; it has even been postulated that the capsular material of the fungus may contain substances the liberation of which can induce malignant transformation. It is even more likely, however, that such a lymphoblastomatous process involving the reticuloendothelial system causes it to fail in the performance of some of its postulated vital duties in the development of immunity and resistance, thereby allowing the infection to become overwhelming.

Infection of the skin is common in cryptococcosis, occurring in perhaps less than 5% of cases In some instances, the skin has been accepted as the portal of entry, although conclusive proof is not presented Most frequently reported has been an acneform eruption of the face, consisting of papules exhibiting a translucency suggesting vesiculation, or
[illegible] rder is
[illegible] lestruc-
[illegible] ulcers
which discharge a tenacious, translucent, grayish or brownish red material, differing markedly from ordinary pus and consisting almost entirely of the encapsulated fungi with little or no cellular contributions from the host. Such ulcers may

be surrounded with an elevated border of some width which has the translucent "pearly" appearance so frequently seen in basal cell carcinomata, with which such lesions have been clinically confused. Similar lesions involving the mucous membranes have been described.

Cryptococcic involvement of bone has been reported by Collins in 17 of some 200 cases. The lesions are multiple and widely disseminated, producing osteolytic rarefactions, especially in bony prominences.

Additionally, lesions have been reported in the kidneys, adrenals, pancreas, testes, bone marrow and large blood vessels. It is considered likely that such involvement occurs more frequently than is actually observed because there may have been no symptoms or signs leading the pathologist to search diligently throughout all such areas of the body as these.

IMMUNOLOGY

[illegible] are striking examples of lack of resistance by phagocytosis The literature contains a few reports of positive reactions to [illegible] and Kaplan reported moderately positive responses, and Evans and Mehl have isolated and purified polysaccharides from 3 types of the fungus, designated as A, B and C, and have utilized them in precipitin and agglutination tests and in capsular reactions, concluding that the capsule is concerned in such type specificity Kligman could not demonstrate any serologic response or dermal reactivity in infected rabbits or mice with any of several preparations Fisher attributed the usual fatal termination of cryptococcosis to poor antibody response and inefficient phagocytosis on the part of the host, and to the protection afforded to the fungus by its capsule Several attempts to utilize vaccines in treatment have been unsuccessful

Therapy

There is no treatment which can be relied on to exert [illegible]

Localized cutaneous or mucous membrane lesions and accessible abscesses or gelatinous cysts may respond to incision and drainage, excision or amputation of an involved limb, especially if assisted by the administration of iodide in large doses and perhaps by x-radiation. A long period of observation is necessary before cure can be assumed.

Based on the observation that cultures of *C. neoformans* do not survive temperatures of 105 to 107F for more than 6 or 7 days, several authors have suggested that artificial fever therapy might be beneficial. There has not as yet been sufficient clinical trial made of this approach to furnish any conclusive evidence of its value. Evidence tending to discourage such hope are the facts that rabbits (which have a high normal temperature) succumb to the infection, and febrile patients die more rapidly than afebrile ones Mosberg, Alvarez and De Choudens advocated combining fever therapy with "alkalinization."

Until better methods are available, a high caloric, high protein diet, supplemental vitamins, especially of the B series, bed rest and the avoidance of steroid hormones is recommended

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